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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,820	10/12/1999	DANIEL G. CHAIN	CHAIN=1B	6495

7590 04/22/2003

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EXAMINER
DUFFY, PATRICIA ANN

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/22/2003

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/402,820	Chain
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 5-23-01.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 14, 23-25, 32-37 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 14, 23-25, 32-37 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3

☐ Interview Summary, PTO-413

☒ Notice of Ref rence(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing R view, PTO-948

☐ Other_____

Office Action Summary

Response to Amendment

1. The amendment filed 10-23-01 has been entered into the record. Claims 14-23-25 and 32-37 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. The rejection of claims 14 and 23-25 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

4. Unless specifically maintained, the art rejections of record are withdrawn in view of the amendments to the claims that now recite "free-end specific" and in view of the new rejections set forth below. Applicants arguments are moot in view of the new rejections set forth below.

Rejections Maintained

5. Claims 23 and 25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Koing et al (Ann NY Acad. Sci., 777:345-355, 1996) or in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al

(BioTechniques, 16(3):476-483, 1994) is maintained for reasons made of record in Paper No. 10, mailed 5-23-01.

The claims are drawn to single chain antibodies that are free-end C-terminal-specific for Aβ peptides.

Koing et al differs by not teaching recombinantly produced single chain antibodies.

Seubert et al teach the use of antibodies that bind Aβ peptides are useful in the diagnosis of probable Alzheimer's disease and are useful for detecting Aβ peptides in *in vitro* or *in vivo* assays that screen for inhibitors of Aβ peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "...the detection techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, V_L, V_H, and other fragments." Seubert et al also teach that "It will also be possible to employ recombinantly produced antibodies (immunoglobulins) and variations thereof as now well described in the patent and scientific literature. See, for example, EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full paragraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of an single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that this invention was made to modify the end-specific monoclonal antibodies of Koing et al (Ann NY Acad. Sci., 777:345-355, 1996) as set forth *supra* by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments including those that have been recombinantly produced that bind Aβ peptides are useful in a variety of detection techniques for use in screening or diagnostic assays.

Applicants argue that Koing et al does not teach that the free-end specific C-terminal Aβ(1-42) monoclonal antibody does not bind the amyloid β-precursor protein from which said amyloid β-peptide may be proteolytically derived. This is not persuasive, Koing et al teaches that antibody staining is limited to plaque structures and "no labeling of neuronal cytoplasm, neurites, intracellular tangles or extracelluar tangles were seen with either antibody in Brodmann's area 22 (see page 349). As such, one skilled in the art would readily appreciate that the monoclonal antibodies did not bind the amyloid β-precursor protein from which said amyloid β-peptide may be proteolytically derived which is present in all cells. Applicants are therefore wrong in asserting that there is no evidence that the monoclonal antibody does not bind the intact APP protein. The rejection is maintained.

New Rejections Based on Amendment

6. Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is rejected for being confusing because each of the alternatives have the same free, N-terminal and as such do not properly represent alternative choices of N-terminal "free ends" because they all are identical.

7. Claims 14 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee-based IDS Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97).

The claim is drawn to a monoclonal antibody that is free-end specific for the free N-terminus of an amyloid β-peptide, which antibody does not bind to the amyloid β-precursor protein form which said amyloid β-peptide may be proteolytically derived.

Saido et al teach a polyclonal antibody 9204, that was produced using a synthetic hexamer peptide DAEFRC (Asp-Ala-Glu-Phe-Arg-Cys) conjugated to keyhole limpet hemocyanin. The antibody distinguish the fragments possessing the exact amino terminus of Aβ from the intact precursors and other fragments including the secretase products. Antibody 9204 also recognized synthetic Aβ1-40 peptide but not Aβ2-40 peptide. Furthermore that binding of AB9204 to APP-C100 was inhibited by the haptenic peptide DAEFRC, but not by MADEFTC or

by AEFRHC. Saido et al teaches that this indicates that the antibody has strict specificity toward the cleavage site with an accuracy of 1 amino acid residue (i.e. the instant free-end specific N-terminal specific). Saido et al teaches that use of the cleavage site specific antibody provides for better relative quantitativeness. (See page 15254-55, column 1, Results , first and second paragraphs). Saido et al teaches that "..similar approaches for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxyl-terminal processing of Aβ peptides....". Saido et al differs by not teaching a monoclonal antibody with the properties of polyclonal antibody 9204.

Takeda et al teach that monoclonal antibodies that are specific for the N-terminal of Aβ (see page 5, first full paragraph, lines 9-20) are useful for the detection of Aβ (1-40) and Aβ (1-42) for the detection of Aβ species *in vitro*.

Goding teaches routine methods of making monoclonal antibodies with defined immunogens.

It would have been prima facie obvious to one having ordinary skill in the art at the time that the invention was made to use the teachings of Saido et al to generate free-end N-terminal specific monoclonal antibodies that do not bind the precursor using the conventional techniques of Goding et al because of the well established advantages of high-affinity, high specificity and unlimited supply that are central to monoclonal antibodies. One would have been motivated to make monoclonal antibodies to decrease the lot to lot variability that can happen with polyclonal antisera and Takeda et alt each that such antibodies are useful for the detection of Aβ (1-40) and

Aβ (1-42) for the detection of Aβ species *in vitro*. One of ordinary skill in the art would have a reasonable expectation of success give the demonstrated immunogenicity of the epitope.

8. Claims 23, 24 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee IDS Nov 16, 2001), Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as applied to claims 14 and 32 above and further in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al (BioTechniques, 16(3):476-483, 1994).

The claims are drawn to single chain antibodies that are free-end N-terminal- end-specific for Aβ peptides and further limited to Aβ(1-40), Aβ (1-42) or Aβ (1-43).

Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) are set forth *supra*. The references as combined fail to teach single chain antibodies.

Seubert et al teach the use of antibodies that bind Aβ peptides are useful in the diagnosis of probable Alzheimer's disease and are useful for detecting Aβ peptides in *in vitro* or *in vivo* assays that screen for inhibitors of Aβ peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "...the detection

techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, V_L, V_H, and other fragments." Seubert et al also teach that "It will also be possible to employ recombinantly produced antibodies (immunoglobulins) and variations thereof as now well described in the patent and scientific literature. See, for example, EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full paragraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of an single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that this invention was made to modify the free-end, N-terminal end-specific monoclonal antibody according to the combination of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994), Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) *supra*, by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments

including those that have been recombinantly produced that bind Aβ peptides are useful in a variety of detection techniques for use in screening or diagnostic assays.

9. Claims 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee IDS of Nov 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97).

The claim is drawn to a monoclonal antibody that is free-end specific for the free C-terminus of an amyloid β-peptide (1-40) or (1-43), which antibody does not bind to the amyloid β-precursor protein form which said amyloid β-peptide may be proteolytically derived.

Saido et al teach a polyclonal antibody 9204, that was produced using a synthetic hexamer peptide DAEFRC (Asp-Ala-Glu-Phe-Arg-Cys) conjugated to keyhole limpet hemocyanin. The antibody distinguishes the fragments possessing the exact amino terminus of Aβ from the intact precursors and other fragments including the secretase products. Antibody 9204 also recognized synthetic Aβ1-40 peptide but not Aβ2-40 peptide. Furthermore that binding of AB9204 to APP-C100 was inhibited by the haptenic peptide DAEFRC, but not by MADEFTC or by AEFRHC. Saido et al teaches that this indicates that the antibody has strict specificity toward the cleavage site with an accuracy of 1 amino acid residue (i.e. the instant free-end specific N-terminal specific). Saido et al teaches that use of the cleavage site specific

antibody provides for better relative quantitativeness. (See page 15254-55, column 1, Results , first and second paragraphs). *Saido et al teaches that "..similar approaches for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxyl-terminal processing of Aβ peptides....".* Saido et al differs by not teaching a monoclonal antibody to the free-carboxyl terminus of Aβ1-40 peptide with similar properties of polyclonal antibody 9204 (i.e. free end specific distinguishing the fragments possessing the exact carboxyl terminus of Aβ from the intact precursors and other fragments including the secretase products.

Takeda et al teach that monoclonal antibodies that are specific for the C-terminal of Aβ (see page 5, first full paragraph, lines 9-20) are useful for the detection of Aβ (1-40) and Aβ (1-42) for the detection of Aβ species *in vitro*. Takeda et al teach the sequence of the free-C-terminal amino acids for Aβ (1-40) and Aβ (1-43).

Seubert et al teach that Aβ42(43)-positive senile plaques are the major species in sporadic disease brain (see column 1, lines 1-3). Seubert et al teach that there is a higher percentage of Aβ(1-42) than Aβ (1-40) in certain inheritable forms of Alzheimer's disease (column 2, lines 29-32).

Goding teaches routine methods of making monoclonal antibodies with defined immunogens.

It would have been prima facie obvious to one having ordinary skill in the art at the time that the invention was made to use the teachings of Saido et al to generate Aβ (1-40) and Aβ (1-43) free-end C-terminal specific monoclonal antibodies that do not bind the precursor using the

conventional techniques of Goding et al and Saido et al because Takeda et alt each that such antibodies are useful for the detection of Aβ (1-40) and Seubert et al teach that Aβ (1-43) is one of the major species in sporadic disease brain and the monoclonal antibodies against these species would be useful for the detection of Aβ species *in vitro* for the diagnosis or detection of Alzheimer's disease and Saido et al teach that similar approaches for producing the proteolytic product specific antibodies will be applicable to resolving the differential carboxyl-terminal processing of Aβ peptides. One of ordinary skill in the art would have a reasonable expectation of success give the demonstrated immunogenicity of the epitopes by the art according to Takeda et al. and Saido et al teach that the unique methodology for producing such proteolytic product specific antibodies now seems to have general applicability and one would have been further motivated to produce monoclonal antibodies because they provide the well established advantages of high-affinity, high specificity and unlimited supply that are central to monoclonal antibodies.

10. Claims 23, 25, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994, Fee IDS of Nob 16, 2001) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) as applied to claims 33 and 34 above and

further in view of Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Duenas et al (BioTechniques, 16(3):476-483, 1994).

The claims are drawn to single chain antibodies that are free-end C-terminal- end-specific for Aβ peptides and further limited to Aβ(1-40) or Aβ (1-43).

Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) are set forth *supra*. The references as combined fail to teach single chain antibodies.

Seubert et al further teach the use of antibodies that bind Aβ peptides are useful in the diagnosis of probable Alzheimer's disease and are useful for detecting Aβ peptides in *in vitro* or *in vivo* assays that screen for inhibitors of Aβ peptide formation (see columns 4-5, Summary of the Invention). Seubert et al teach that in addition to monoclonal antibodies, "...the detection techniques of the present invention will also be able to use antibody fragments, such as F(ab), Fv, V_L, V_H, and other fragments." Seubert et al also teach that "It will also be possible to employ recombinantly produced antibodies (immunoglobulins) and variations thereof as now well described in the patent and scientific literature. See, for example, EPO 8430268.0; EPO 85102665.8; EPO 85305604.2; PCT/GB 85/00392; EPO 85115311.4; PCT/US 86/002269; and Japanese application 85239543." (see column 10, first full paragraph).

Duenas et al teach art accepted conventional methods of intra- and extracellular expression of an single chain Fv antibody fragment (scFv) in *E. coli*. Duenas et al teach that cloning of immunoglobulin variable regions and bacterial expression of antibody fragments was routinely performed in the art at the time that this invention was made (see page 476, column 2, Introduction).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time that this invention was made to modify the free-end, C-terminal end-specific monoclonal antibody according to the combination of Saido et al (The Journal of Biochemistry, 269(21):15253-15257, 1994) in view of Takeda Chemical Industries Ltd., (EP 0 683 234 A1, published November 22, 1995, reference AC on PTOL-1449 filed 12 October 1999), Seubert et al (U.S. Patent 6,114,133, issued September 5, 2000 and filed November 14, 1994) and Goding (Monoclonal Antibodies, Academic Press Inc., London 1983, pages 56-97) *supra*, by means of expression as a single chain Fv antibody fragment (scFv) according to the vectors and methodology of Duenas et al because Seubert et al teach that Fv and other antibody fragments including those that have been recombinantly produced that bind Aβ peptides are useful in a variety of detection techniques for use in screening or diagnostic assays.

Status of Claims

11. All claims stand rejected.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
April 20, 2003

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600